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FURTHER STUDIES ON THE EFFECTS OF THE ROENTGEN RAY ON ANTIBODY- PRODUCTION

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In a previous paper¹ are given the results of observations on the influence of the roentgen ray on the production of lysin for sheep corpuscles in the white rat. It was found that prolonged exposure to roentgen ray, about the time the antigen was injected, markedly reduced the production of lysin, due, it was assumed, to destructive action on the lymphatic tissues, the spleen, and the marrow. In order to test the effect of the ray on antibody-production after it is well under way, that is, a few days after the introduction of the antigen, it proved advisable to use animals that would stand repeated bleedings better than the rat. The purpose now is to present briefly the results of experiments of this and like nature on the dog and the rabbit.

In these experiments, the only variation in the treatment with roentgen ray was in the length of exposure. The radiation was always made with the Coolidge tube, the focal distance always 8 inches, the current 5 to 6 milliamperes, spark-gap 8 inches. The exposures were made in the roentgen-ray laboratory of the Presbyterian Hospital, under the direction of Dr. J. W. Rowntree, to whom I am indebted very much. Young animals were used, dogs a few weeks old, and rabbits weighing about 1000 gm.

As a rule 2 exposures were made, a major followed by one one-fourth as long the next day immediately before the injection of the antigen. In the dogs, the antigen, 1 c.c. 10% suspension of rat or goat blood per kilo of weight of dog, was injected intravenously; in the rabbit, 25 c.c. of sheep blood were injected intraperitoneally. Only one injection of antigen was given. In the dog, the antibodies measured were the agglutinin and opsonin for rat corpuscles and the lysin for goat corpuscles; in the rabbits, the titers of the lysin for sheep corpuscles and of the precipitin for sheep blood proteins were determined. The figures in the tables give the highest active dilutions of the serum in the case of the agglutinin, opsonin and lysin tests, and the highest dilution of sheep blood, in which the rabbit serum produced precipitate by the ring or contact method in the case of the precipitin tests. The details of making the tests are described in previous articles.²

Received for publication July 17, 1917.

¹ Jour. Infect. Dis., 1915, 17, p. 415.

² Ibid., 1910, 7, p. 319; 1914, 14, p. 403; 1916, 19, p. 69.

EFFECT OF ROENTGEN RAY AT THE BEGINNING OF ANTIBODY-
PRODUCTION

The results of new experiments on the action of roentgen ray at the beginning of antibody-production are illustrated in the instances from various experiments brought together in Tables 1 and 2. Table 1 shows that in dogs (Dogs 2 and 5) treated in the manner I have indicated, a marked reduction in the output of antibodies is obtained by a 10-minute exposure followed the next day by a 2½-minute exposure (approximately 37½ Kienbach units). In dogs so treated, there

TABLE 1
EFFECT OF THE ROENTGEN RAY ON THE DEVELOPMENT OF ANTIBODIES IN THE DOG

Days After Infection of Antigen	Injected With Rat Blood			Injected With Goat Blood			Remarks
	Dog 1; Roent- gen Ray 2½ min., the Next Day 40 sec.	Dog 2; Roent- gen Ray 10 min., the Next Day 2½ min.	Dog 3; Roent- gen Ray 20 min., the Next Day 5 min.	Dog 4; Roent- gen Ray 2½ min., the Next Day 40 sec.	Dog 5; Roent- gen Ray 10 min., the Next Day 2½ min.	Dog 6; Roent- gen Ray 20 min., the Next Day 5 min.	
2	24			96			
4	24	96	0	192	192	48	Leukocytes: Dog 3-3600, Dog 6-2200
6	192	768	0	384	768	96	Leukocytes: Dog 3-3000, Dog 6-2400
8	1536	768	0	6144	1536	96	Leukocytes: Dog 3-1800, Dog 6-3000
10	3072	384	24	6144	1536	96	
12	3072	384	96	6144	1536	96	Leukocytes: Dog 3-1500, Dog 6-2100
14	3072	384		1536	768		
16	3072		96	1536		96	Marked Roentgen-ray burns in Dogs 5 and 6
18		142			384		
20	1536			768			
22	768	192		768	24		
24							
26	96			96			
28							
30	96			96			

may be only little apparent disturbance of the general health and no great change in the leukocytes in the peripheral blood; an occasional animal succumbs, however, and there may be then marked roentgen-ray effects. Dogs 3 and 6, Table 1, illustrate that treatment with roentgen ray for 20 minutes and again for 5 minutes the next day (75 Kienbach units) may restrain practically completely all production of antibodies in response to antigen injected immediately after the 2d exposure. In such animals, there is usually reduction in the leukocytes in the blood with relative decrease in the granular and relative increase in the nongranular forms; severe burns may develop, and

the thymus, spleen, and marrow show evidences of cell destruction. Dogs 1 and 4, Table 1, appear not to have suffered any loss of power to elaborate antibodies, as the result of exposures to roentgen ray for 21½ minutes and then for 40 seconds (91½ Kienbach units), the course and quantity of antibodies produced by these animals correspond to normal standards.

The rabbit is less satisfactory to work with than the dog because of the much higher death rate and the much greater individual variation in response to antigen. As shown in Table 2, however, results are obtained which correspond to those in the white rat and the dog.

TABLE 2
EFFECT OF THE ROENTGEN RAY ON THE DEVELOPMENT OF ANTIBODIES IN THE RABBIT

Days After Injection of Sheep Blood	Rabbit 1; Roentgen Ray 10 min., the Next Day 2½ min.		Rabbit 2; Roentgen Ray 5 min., the Next Day 1½ min.		Rabbit 3; Roentgen Ray 2 min., the Next Day ½ min.		Control		Remarks
	Lysin	Precip- itin	Lysin	Precip- itin	Lysin	Precip- itin	Lysin	Precip- itin	
5	512	0	2048	0	4096	0	768	0	In Rabbit 1, the leukocytes came down to 1400 with a late relative decrease in granular and relative in- crease in non- granular leu- kocytes. In Rabbits 2 and 3, no definite change in leukocytes
8	2048	400	8192	800	8192	800	6144	800	
10	6144	400	3072	400	8192	6400	12288	3200	
12	3072	1200	6144	800	24576	12800	12288	6400	
14	1536	1200	3072	800	12288	6400	6144	12800	
16	1536	800	1536	800	6144	6400	3072	12800	
19	1536	400	3072	800	6144	4800	3072	12800	
22	1536	800	3072	800	6144	4800	3072	12800	
26	1536	200	1536	400	6144	1600	3072	12800	
30	768	200	768	400	1536	1600	3072	3200	
35	1536	400	768	800	1536	1600	3072	3200	
41	768	200	768	400	3072	1600	1536	1600	
45	1536	800	768	400	3072	1600	1536	1600	
51	768	200	384	400	3072	1600	1536	1600	
62	192	400	192	400	1536	1600	1536	800	
89	192	400	384	200	1536	400	768	200	

EFFECT OF THE ROENTGEN RAY AT OR NEAR THE HEIGHT OF
ANTIBODY-PRODUCTION

In this series of animals, in which the manufacture of antibodies was well under way, were exposed to roentgen ray and an effort made to determine whether this would affect the subsequent course of the antibodies in the blood. Table 3, which is representative of several experiments of this kind, appears to show that a 20-minute exposure on the 7th day after the injection of the antigen had no demonstrable effect, as the antibodies continue to run their course precisely as in dogs injected in the same way, but not put under the influence of the ray. Even when combined with splenectomy exposure to roentgen

ray at or near the height of the antibody output seems to have no effect on the height and course of the curve. It is noteworthy that in many of the animals exposed to the ray for 15-20 minutes after the introduction of the antigen, the general health did not suffer any marked disturbances, and there developed, as shown in Table 3, only a moderate degree of leukopenia. In one dog, there developed, however, a marked leukopenia—900 on the 6th day after exposure to the ray, 650 on the 14th, 800 on the 21st, 500 on the 27th. It died on the 28th day after the exposure; there was marked anemia and emaciation; the thymus was represented by a few pinkish spots, the spleen greatly shrunk, the marrow poor in cells, and the stomach and intestine thin

TABLE 3
EFFECT OF ROENTGEN RAY AT HEIGHT OF ANTIBODY-PRODUCTION IN DOGS

Days After Injection of Antigen	Injected with Rat Blood		Injected with Goat Blood, Dog 3	Remarks
	Dog 1	Dog 2		
4	192	384	3072	Roentgen Ray for 20 minutes
5	384	384	6144	
6	1536	1536	12288	
7	1536	1536	12288	
8	1536	1536	12288	
9	3072	1536	12288	
10	1536	3072	6144	
11	1536	1536	6144	
12	3072	3072	3072	
13	3072	3072	6144	
14	1536	1536	3072	Leukocytes: Dog 1-10000, 2-13400, 3-6800
15	1536	1536	1536	Leukocytes: Dog 1-9200, 2-8000, 3-7800
16	1536	768	768	Leukocytes: Dog 1-4900, 2-6000, 3-5400
18	1536	1536	768	Leukocytes: Dog 1-7000, 2-3000, 3-6800
22	384	384	768	Leukocytes: Dog 1-6200, 2-4000, 3-5000
30	768	384	768	Leukocytes: Dog 1-5100, 2-2500, 3-5200
38	384	96	768	Leukocytes: Dog 1-4800, 2-3600, 3-6800
42	192	96	96	Leukocytes: Dog 1-10600, 2-6200, 3-7200

and distended. But there was no reduction in the amount of lysin for goat corpuscles or irregularities in its course as compared with the amount and course in the control animal.

It would require many more experiments than I have made to determine conclusively whether animals in the stage of active antibody—production, as a rule, have an increased resistance to roentgen-ray effects. The results at hand indicate that such may be the case.

It is of much interest because it bears directly on this problem that benzene, which in many ways acts like the roentgen ray, appears to have no leukopenic effect in rabbits when given in the period of antibody-production in quantities otherwise usually effective.³

* Jour. Infect. Dis., 1916, 19, p. 69; p. 737.

In rabbits, too, roentgen ray about the 15th day after the injection of the antigen has not had in my experiments so far any definite effect on the course of the specific antibodies.

In the dog, the failure of the roentgen ray to restrain the production of antibodies after it is under way might be explained as due to the lapse of time before the radiation becomes effective, the elaboration of antibodies in the meantime passing the acme and entering on a natural decline; but it may be assumed, with at least equal reason, that the failure depends on an actual increase in the resistance to the usual roentgen-ray effects. In the rabbit, the period of active antibody-production appears much longer than in the dog, at least under the circumstances of these experiments, and consequently the first explanation suggested of the failure of the roentgen ray does not seem applicable at all to the failure of benzene to depress the antibody output when given some time after the antigen. Assuming that there develops an increased resistance to benzene and to roentgen ray, as the production of antibodies proceeds, the question arises, what is the nature of this resistance? We might adopt the hypothesis that the biologic effects of these agents are due to their influence on enzymes, as asserted by Richards⁴ for radioactivity; and that, in the course of active antibody-production, special enzymes accumulate to such extent that the roentgen ray or benzene does not affect them appreciably. Whether it proves possible to furnish evidence from experiment in support of some such hypothesis as this remains to be seen.

Here I would point out that the interference of the roentgen ray under certain circumstances with the elaboration of antibodies may be a factor in the rapid development of tuberculosis in roentgenized guinea-pigs. Recently Morton⁵ pointed out that this effect of the ray may be of practical value in hastening the diagnosis by guinea-pig inoculation in renal tuberculosis.

The failure of the ray to reduce the antibody-content of the blood after it has reached a certain concentration recalls the experiments of Kessel and Sittenfeld⁶ on radiation in the later stages of inoculation tuberculosis in guinea-pigs. The results appear to indicate that in this case radiation tends to prolong life and to promote healing of lesions. It seems then as if the effects of the roentgen ray is different not only

⁴ Science, 1915, 42, p. 287.

⁵ Jour. Exper. Med., 1916, 24, p. 419. See also Murphy and Taylor: Ibid., 25, p. 609.

⁶ Proc. N. Y. Path. Soc., 1914, 14, p. 190.

in the early and the later phases of antibody production, but also in the early and later stages of experimental tuberculosis in guinea-pigs. This is a suggestive parallelism that merits further study.

SUMMARY

Exposure of dogs and rabbits to the roentgen ray at about the same time as antigen is introduced may restrain in high degree, and under some conditions completely, the production of antibodies as measured by the antibody content of the serum. The results correspond fully to those previously obtained from experiments on the white rat.

When antibody-production is at or near its height, exposure to the roentgen ray appears to have but little if any effect on the antibodies in the blood, and at this time dogs appear to have an increased resistance to the effects of the ray just as rabbits in the period of active production of antibodies have an increased resistance to effects of benzene. Whether there is any relationship between this apparent resistance to the effects of roentgen rays and the reported beneficial effect of the rays in the later stages of tuberculosis in guinea-pigs remains to be determined.

As stated previously¹ the results obtained from these observations harmonize with the view that antibodies are produced in the spleen, lymphatic tissues, and marrow, as these structure suffer most directly from the action of the roentgen ray; they indicate also that one reason why the lymphocyte appears to be an important agent of defense in tuberculosis and other conditions may be its power to form antibodies and that the rapid development of tuberculosis in roentgen-rayed guinea-pigs may depend, at least in part, on interference with antibody-production.